Date of Approval Letter:

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-338

NAXCEL Sterile Powder
(ceftiofur sodium)

To establish a 4-day pre-slaughter withdrawal time for swine

Sponsored by:
Pharmacia & Upjohn Company
A Division of Pfizer Inc

1. *GENERAL INFORMATION:*

a. File Number:	NADA 140-338
b. Sponsor:	Pharmacia & Upjohn Co. 7000 Portage Road Kalamazoo, MI 49001-0199 Drug Labeler Code: 000009
c. Established Name:	Ceftiofur sodium
d. Proprietary Name:	NAXCEL Sterile Powder
e. Dosage Form:	Sterile powder for reconstitution to injectable solution
f. How Supplied:	1 and 4 g glass vial
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	50 mg ceftiofur equivalents (CE) per mL of reconstituted solution
i. Route of Administration:	Intramuscular (IM) injection
j. Species/Class:	Swine
k. Recommended Dosage:	1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lb of body weight). Treatment should be repeated at 24 h intervals for a total of three consecutive days.
l. Pharmacological Category:	Antimicrobial
m. Indications:	NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis* type 2.
n. Effect of Supplement:	To establish a 4-day pre-slaughter withdrawal time for swine

2. *EFFECTIVENESS:*

This supplement to NADA 140-338 does not change the effectiveness data for this product.

3. *TARGET ANIMAL SAFETY:*

This supplement to NADA 140-338 does not change the target animal safety data for this product.

4. *HUMAN FOOD SAFETY:*

A. Toxicology

Complete summaries of all pivotal toxicology studies of ceftiofur pertaining to human food safety are found in the original Human Safety Section of the Freedom of Information Summaries for NADA 140-338 and NADA 141-235 (ceftiofur crystalline free acid, EXCEDE for Swine Sterile Suspension). As described in the Freedom of Information Summary for NADA 141-235, CVM interpreted the results of the Acute Single Dose Intake (ASDI) study summarized in NADA 140-338 to establish a safe concentration of 166 ppm for injection site muscle.

B. Residue Chemistry

The total residue depletion and metabolism data in the target species and comparative metabolism data in the toxicological species for ceftiofur are summarized in the FOI Summaries for NADA 140-338 and NADA 140-890 (ceftiofur hydrochloride, EXCENEL RTU Sterile Suspension). The marker residue in edible tissues is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by HPLC as the stable derivative desfuroylceftiofur acetamide (DCA). The target tissue for residue monitoring is kidney and the tolerance is 0.25 ppm. The following pivotal study was conducted to determine the withdrawal period.

1) **Title:** Decline of ceftiofur and desfuroylceftiofur-related residues in swine tissues after intramuscular administration of ceftiofur sodium (NAXCEL Sterile Powder) to swine at a rate of 5 mg ceftiofur equivalents/kg body weight for three consecutive days (Study Report No. a0100487, 12 March 2002).

   Principal Investigators: D.A. Merritt & M.J. Prough, Pharmacia Animal Health, Kalamazoo, MI.

   Animal Species: swine.

   Breed/Sex: Yorkshire mixed-breed/male and female in equal numbers.

   Number of Animals: 36.

   Health Status: clinically healthy.

Route of Administration: intramuscular (IM).

Dose Rate: 5 mg of ceftiofur equivalents/kg body weight.

Duration of Dosing: 1 treatment per day at approximately 24-hour intervals for three consecutive days.

Marker Residue Depletion Data: Kidney tissues were collected from six animals at each time point of 3, 24, 48, 72, 96, and 120 hours after the three-day treatment period and were assayed for desfuroylceftiofur-related residue by the HPLC-DCA regulatory assay. This provided kidney residue concentration information as summarized in the following table.

Concentration of Desfuroylceftiofur-related Residue by the HPLC-DCA Assay in Swine Following 3 Days of IM Treatment of NAXCEL Sterile Powder at 5 mg ceftiofur/kg/day

Slaughter Interval, (hours)	Concentration, µg/g * (Mean ± SD)
	Kidney
3	5.4 ± 1.1
24	1.1 ± 0.2
48	0.38 ± 0.09
72	0.18 ± 0.06
96	(0.073) ± 0.012
120	(<LOD-0.067)

* LOQ = 0.10 µg/g, LOD = 0.050 µg/g. Values <LOQ but >LOD are listed in parentheses.

2) Withdrawal Period

The data from the study above were analyzed by a statistical method which determines the statistical tolerance limit for the 99th percentile of the population with a 95% confidence. At 4 days, the upper 95 percent confidence limit on the 99th percentile for kidney residues was less than the kidney tolerance (0.25 ppm). These data support a 4-day pre-slaughter withdrawal period after intramuscular administration of NAXCEL Sterile Powder in swine when used according to label directions.

C. Microbial Food Safety

This NADA supplement establishes a 4-day pre-slaughter withdrawal period for swine. Because this change to NADA 140-338 does not change the product indication, dose,

dose duration, or other conditions of use beyond the addition of a withdrawal period, an evaluation of Microbial Food Safety was determined not to be necessary at this time for the supplemental approval to this product.

D. Regulatory Method for Residues

The regulatory method for determination of DCA in swine kidney and muscle, and bovine kidney, muscle, and milk is the HPLC-DCA assay which successfully completed a sponsor-monitored multi-laboratory method trial. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

5. *USER SAFETY:*

Studies to evaluate the safety of ceftiofur to users are discussed in detail in the original FOI Summary for NADA 140-338.

Human Warnings are provided on the product labeling as follows:

Not for human use. Keep out of reach of children.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or obtain a material safety data sheet, call 1-800-253-8600.

6. *AGENCY CONCLUSIONS:*

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that NAXCEL Sterile Powder, when administered according to the label directions, is safe and effective for the treatment and control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis* type 2.

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay

persons to appropriately diagnose and subsequently use this product to treat swine respiratory disease, (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues, and (c) the rate of emergence of ceftiofur-resistant organisms may be reduced by the involvement of veterinarians in product use.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

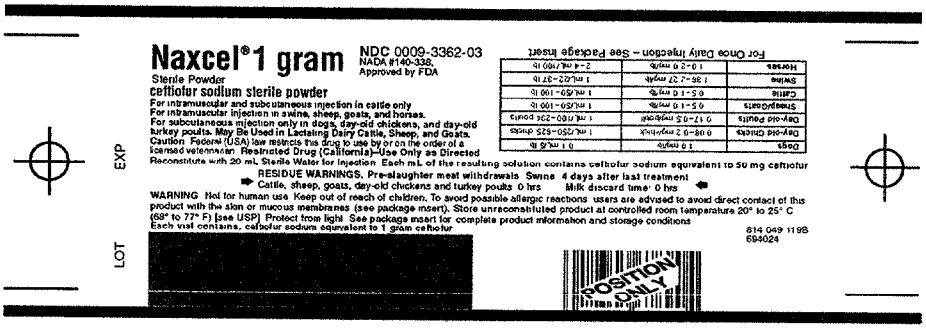
In accordance with the Center's supplemental approval policy 21 CFR 514.106(b)(2)(x), this is a Category II change which did not require a reevaluation of safety and effectiveness data in the parent application.

No patents were submitted with this application.

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

A. NAXCEL Sterile Powder - 1 g vial and shipper carton label
B. NAXCEL Sterile Powder - 4 g vial and shipper carton label
C. NAXCEL Sterile Powder - package insert



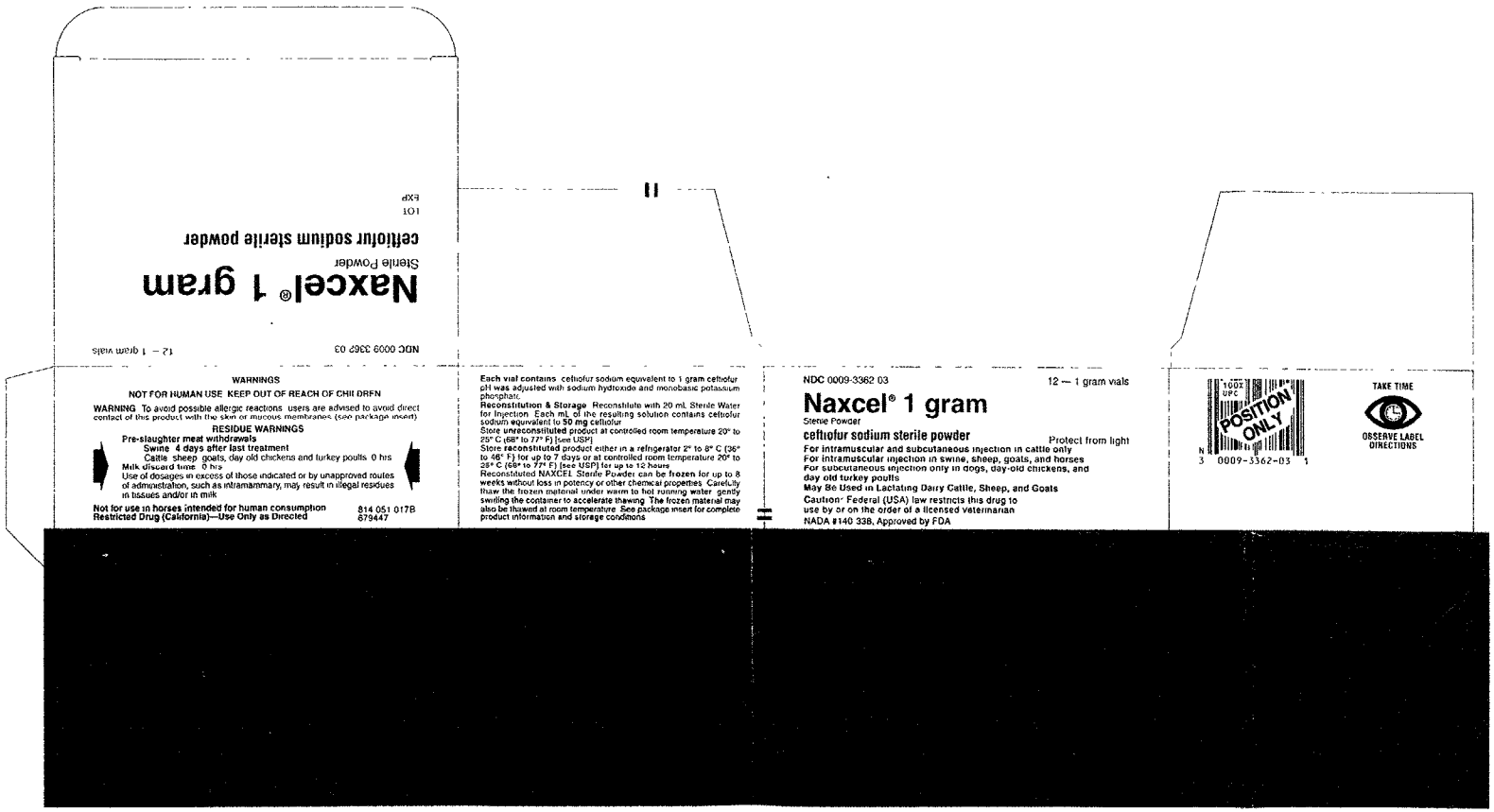
Pfizer

Black | PMS 032

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23044	NAXCEL 1 gram		814 049 119B
CCS #	NDC #	EDP #	ITEM
3362-03	0009-3362-03		Label
BOTTLE #	SIZE	IMPRINT SIZE	DRAWING #
	3.6875 x 1.3125 inches	Left side	
ADDITIONAL INFORMATION		DATE	TYPESET BY
		02/24/04	L. Amos

Pantone® colors used in this proof may not match the Pantone® solid color standards. Use current Pantone® swatch guide for most accurate color.



Pfizer

Composition Unit 2566

COMPOSITION ORDER # 23045	PRODUCT NAXCEL 1 gram		COPY CODE # 814 051 017B
CODE # 3362-03	TYPE # 0009-3362-03	SIZE #	ITEM Carton
BOTTLE #	SIZE 131.5 x 100 x 70 mm	TAPE PART SIZE	CARTON #
ADDITIONAL INFORMATION NO VARNISH IN THE IMPRINT AREA		DATE 02/24/04	APPROVED BY L. Amos

Pantone® colors used on this proof may not match the Pantone® solid color standards. Use current Pantone® swatch guide for most accurate color.

Naxcel® 4 grams

Sterile Powder

ceftiofur sodium sterile powder

NDC 0009-3362-04

NADA #140-338, Approved by FDA

For intramuscular and subcutaneous injection in cattle only.
For intramuscular injection in swine, sheep, goats, and horses.
For subcutaneous injection only in day-old chickens, and day-old turkey poults.
May Be Used in Lactating Dairy Cattle, Sheep, and Goats.

For Once Daily Injection – See Package Insert

Horses	1.0–2.0 mg/lb	2–4 mL/100 lb
Day-old Chicks	0.08–0.2 mg/chick	1 mL/250–625 chicks
Sheep/Goats	0.5–1.0 mg/lb	1 mL/50–100 lb
Cattle	0.5–1.0 mg/lb	1 mL/50–100 lb
Swine	1.36–2.27 mg/lb	1 mL/22–37 lb
Day-old Poults	0.17–0.5 mg/poult	1 mL/100–294 poults

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. **Restricted Drug (California)–Use Only as Directed**
Reconstitute with 80 mL Sterile Water for Injection. **Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.**

RESIDUE WARNINGS: Pre-slaughter meat withdrawals: Swine: 4 days after last treatment.
Cattle, sheep, goats, day-old chickens and turkey poults: 0 hrs. **Milk discard time:** 0 hrs.

WARNING: Not for human use. Keep out of reach of children. To avoid possible allergic reactions, users are advised to avoid direct contact of this product with the skin or mucous membranes (see package insert). Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]. Protect from light. See package insert for complete product information and storage conditions. **Each vial contains:** ceftiofur sodium equivalent to 4 grams ceftiofur

EXP

LOT

814 057 120B
694025

POSITION ONLY

Pfizer

Composition Unit 2566

Black | PMS 032

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23043	NAXCEL 4 grams		814 057 120B
CCS #	**NDC #**	**EDP #**	**ITEM**
3362-04	0009-3362-04		Label
BOTTLE #	**SIZE**	**IMPRINT SIZE**	**DRAWING #**
	6.125 x 2	Left side	
ADDITIONAL INFORMATION		**DATE**	**TYPESET BY**
		02/24/04	L. Amos

Pantone® colors used in this proof may not match the Pantone® solid color standards Use current Pantone® swatch guide for most accurate color

LOT
EXP

ceftiofur sodium sterile powder

Sterile Powder

Naxcel® 4 grams

NDC 0009-3362-04 6—4 gram vials

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN

WARNING To avoid possible allergic reactions, users are advised to avoid direct contact of this product with the skin or mucous membranes (see package insert)

RESIDUE WARNINGS

Pre-slaughter meat withdrawals:
Swine, 4 days after last treatment
Cattle, sheep, goats, day-old chickens and turkey poults 0 hrs
Milk discard time 0 hrs
Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in tissues and/or in milk

Not for use in horses intended for human consumption
Restricted Drug (California)—Use Only as Directed

814 059 01/B
679448

Each vial contains ceftiofur sodium equivalent to 4 grams ceftiofur, pH was adjusted with sodium hydroxide and monobasic potassium phosphate

Reconstitution & Storage Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur

Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]

Store **reconstituted** product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) [see USP] for up to 12 hours

Reconstituted NAXCEL Sterile Powder can be frozen for up to 8 weeks without loss in potency or other chemical properties. Carefully thaw the frozen material under warm to hot running water, gently swirling the container to accelerate thawing. The frozen material may also be thawed at room temperature

See package insert for complete product information and storage conditions

NDC 0009-3362-04 6—4 gram vials

Naxcel® 4 grams

Sterile Powder

ceftiofur sodium sterile powder Protect from light

For intramuscular and subcutaneous injection in cattle only
For intramuscular injection in swine, sheep, goats, and horses.
For subcutaneous injection only in day-old chickens, and day-old turkey poults.
May Be Used in Lactating Dairy Cattle, Sheep, and Goats

Caution. Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian

NADA #140-338, Approved by FDA

TAKE TIME

OBSERVE LABEL DIRECTIONS

POSITION ONLY

N 3 0009-3362-04 8

[redacted]

Pfizer

Composition Unit 2566

23042	NAXCEL 4 grams		814 059 0178
3362-04	0009-3362-04		Carton
	133 x 102 x 70 mm		
NO VARNISH IN THE IMPRINT AREA		02/24/04	L Amos

Naxcel®

brand of ceftiofur sodium
sterile powder

Pharmacia &Upjohn

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats

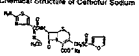
CAUTION Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram positive and gram-negative bacteria including β-lactamase-producing strains Like other cephalosporins ceftiofur is bactericidal in vitro resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur The pH was adjusted with sodium hydroxide and monobasic potassium phosphate

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5 Thia 1 azabicyclo[4 2 0]oct 2 ene 2 carboxylic acid 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino] 3-[[(2 furanylcarbonyl) thio] methyl]-8-oxo- monosodium salt [6R [6α 7β (Z)]]

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows

1 gram vial—Reconstitute with 20mL Sterile Water for Injection Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur

4 grams vial—Reconstitute with 80mL Sterile Water for Injection Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur

STORAGE CONDITIONS

Store unreconstituted product at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]

Store reconstituted product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) [see USP] for up to 12 hours

Protect from light Color of the cake may vary from off white to a tan color Color does not affect potency

ONE-TIME SALVAGE PROCEDURE FOR RECONSTITUTED PRODUCT

At the end of the 7 day refrigerator or 12 hour room temperature storage period following reconstitution, any remaining reconstituted product may be frozen for up to 6 weeks with no loss in potency or other chemical properties This is a one time, only salvage procedure for the remaining product To use the salvaged product at any time during the 6 week storage period hold the vial under cold running water, gently swirling the container to accelerate thawing, or allow the frozen product to thaw at room temperature Rapid freezing or thawing may result in vial breakage Any product not used immediately upon thawing should be discarded

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2 These followed NCCLS Guidelines (National Committee for Clinical Laboratory Standards)

Table 1 Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC$_{50}$ (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	461	1988-1992	0 06	≤0 03-0 13
	Mannheimia haemolytica	42	1993	0 215	≤0 003-0 03
	Pasteurella multocida	319	1988-1992	0 06	≤0 03-0 25
	Pasteurella multocida	48	1993	≤0 002	≤0 003-0 015
	Haemophilus somnus	109	1988-1992	0 06	≤0 03-0 13
	Haemophilus somnus	59	1993	≤0 0015	no range
	Fusobacterium necrophorum	17	1994	≤0 06	no range
Swine	*Actinobacillus pleurop.*	93	1993	≤0 03	≤0 03-0 06
	Pasteurella multocida	74	1993	≤0 03	≤0 03-0 06
	Streptococcus suis	94	1993	0 25	≤0 03-1 0
	Salmonella choleraesuis	50	1993	1 0	1 0-2 0
	beta-hemolytic *Streptococcus* spp	24	1993	≤0 03	≤0 03-0 06
	Actinobacillus suis	77	1996	0 0078	0 0016-0 0078
	Haemophilus parasuis	76	1996	0 06	0 0039 0 25
Sheep	*Mannheimia haemolytica*	39	1992	0 13	≤0 03-0 13
	Pasteurella multocida	23	1992	≤0 03	no range
Canine	*Escherichia coli*	44	1992	4 0	0 06-64 0
	Escherichia coli	16	1990	0 25	0 13-0 5
	Proteus mirabilis	17	1990	≤0 06	≤0 06-0 5
	Proteus mirabilis	23	1992	1 0	≤0 06-4 0
Turkey	*Escherichia coli*	1204	1995	1 0	0 13->32 0

*Minimum inhibitory concentration (MIC) for 90% of the isolates

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brand of ceftiofur sodium sterile powder

Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Animal	Organism	Number Tested	Date Tested	MIC$_{50}$ (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	110	1997 1998	0 06	≤0 03-0 25
	Mannheimia haemolytica	139	1998-1999	≤0 03	≤0 03-0 5
	Mannheimia haemolytica	209	1999-2000	≤0 03	≤0 003-0 12
	Mannheimia haemolytica	189	2000-2001	≤0 03	≤0 003-0 12
	Pasteurella multocida	107	1997-1998	≤0 03	≤0 03-0 25
	Pasteurella multocida	181	1998-1999	≤0 03	≤0 03-0 5
	Pasteurella multocida	206	1999-2000	≤0 03	≤0 003-0 12
	Pasteurella multocida	259	2000-2001	≤0 03	≤0 003-0 12
	Haemophilus somnus	46	1997-1998	≤0 03	≤0 03-0 25
	Haemophilus somnus	87	1998 1999	≤0 03	≤0 003-0 125
	Haemophilus somnus	77	1999-2000	≤0 03	≤0 03-0 06
	Haemophilus somnus	129	2000-2001	≤0 03	≤0 03-0 12
	Bacteroides fragilis group	29	1994	16 0	≤0 06->16 0
	Bacteroides spp., non-*fragilis* group	12	1994	16 0	0 13->16 0
	Peptostreptococcus anaerobius	12	1994	2 0	0 13-2 0
Swine	*Actinobacillus pleurop.*	97	1997 1998	≤0 03	no range
	Actinobacillus pleurop.	111	1998 1999	≤0 03	≤0 03-0 25
	Actinobacillus pleurop.	126	1999-2000	≤0 03	≤0 03-0 06
	Actinobacillus pleurop.	89	2000-2001	≤0 03	≤0 03-0 06
	Pasteurella multocida	114	1997 1998	≤0 03	≤0 03-1 0
	Pasteurella multocida	147	1998-1999	≤0 03	≤0 03 0 5
	Pasteurella multocida	173	1999-2000	≤0 03	≤0 03-0 06
	Pasteurella multocida	186	2000-2001	≤0 03	≤0 03 0 12
	Streptococcus suis	106	1997 1998	0 5	≤0 03-4 0
	Streptococcus suis	142	1998 1999	0 25	≤0 03 1 0
	Streptococcus suis	146	1999-2000	0 06	≤0 03-4 0
	Streptococcus suis	167	2000-2001	0 06	≤0 03-4 0
	Salmonella choleraesuis	96	1999-2000	1 0	0 03->4 0
	Salmonella choleraesuis	101	2000-2001	1 0	0 5 2 0
Equine	*Streptococcus equi subsp. equi*	12	1994	≤0 0019	no range
	Streptococcus equi subsp. equi	29	2002	≤0 03	≤0 03-0 06
	Streptococcus zooepidemicus	48	1994	≤0 0019	no range
	Streptococcus zooepidemicus	59	2002	≤0 03	≤0 03 0 25
	Rhodococcus equi	66	1998	4 0	≤0 03 16 0
	Rhodococcus equi	42	2002	8 0	≤0 03->32 0
	Bacteroides fragilis group	32	1995	>16 0	0 13->16 0
	Bacteroides spp. non-*fragilis* group	12	1995	4 0	0 25-4 0
	Fusobacterium necrophorum	18	1995	≤0 06	no range
Canine	*Escherichia coli*	26	2000	32	0 25 >32
	Proteus mirabilis	14	2000	0 25	0 06 0 25
Turkey	*Escherichia coli*	17	1995 1999	1 0	0 26 1 0
	Escherichia coli	25	1999-2000	0 50	0 12-0 5
	Escherichia coli	20	2000-2001	2 0	0 12 16 0
	Citrobacter spp	37	1995	32 0	0 5->32 0
	Enterobacter spp	51	1995	>32 0	0 13->32 0
	Klebsiella spp	100	1995	1 0	0 13 2 0
	Proteus spp.	19	1995	1 0	0 06-32 0
	Pseudomonas spp.**	31	1995	>32 0	0 06->32 0
	Salmonella spp	24	1995	1 0	0 5-1 0
	Staphylococcus spp (coagulase positive)	17	1995	2 0	1 0-2 0
	Staphylococcus spp (coagulase negative)	26	1995	8 0	0 13->32 0

(continued)

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Animal	Organism	Number Tested	Date Tested	MIC$_{50}$** (µg/mL)	MIC Range (µg/mL)
Chicken	*Escherichia coli*	62	1997 1998	0 50	0 25-2 0
	Escherichia coli	59	1998 1999	4 0	0 25->4 0
	Escherichia coli	87	1999-2000	0 50	0 12 16 0
	Escherichia coli	90	2000-2001	1 0	≤0 03-8 0

* The following in vitro data are available but their clinical significance is unknown
Minimum inhibitory concentration (MIC) for 90% of the isolates.
MIC$_{50}$ is 32 µg/mL

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1 36 to 2 27 mg ceftiofur equivalents/lb (3 0 to 5 0 mg/kg) BW (swine) or 0 5 to 1 0 mg ceftiofur equivalents/lb (1 1 to 2 2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by NCCLS

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2 0	(S) Susceptible
18-20	4 0	(I) Intermediate
≤ 17	≥ 8 0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2 2 mg/kg) BW, clinical effectiveness data and MIC data the following breakpoint is recommended by NCCLS

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0 25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs MIC) cannot be performed These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population

Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain Ceftiofur sodium drake or powder reference standard is appropriate for both test and quality

Table 3 Acceptable quality control ranges for ceftiofur against National Committee for Clinical Laboratory Standards recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter* (mm)	MIC Range (µg/mL)
Escherichia coli (25922)	29-31	0 25-1 0
Staphylococcus aureus (29213)	—	0 25-1 0
Staphylococcus aureus (25923)	27-31	—
Pseudomonas aeruginosa (27853)	14-18	16 0-64 0
Actinobacillus pleuropneumoniae (27090)	34-42	0 004-0 015 **
Haemophilus somnus (700025)	36-46	0 0005-0 004**

* All testing performed using a 30µg disk
** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller Hinton agar Incubated in 5 7% CO_2 for 20 24 hours
MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM)

CATTLE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever pneumonia) associated with *Mannheimia haemolytica Pasteurella multocida* and *Haemophilus somnus* NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*

Dosage and Administration

Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0 5 to 1 0 mg ceftiofur per pound of body weight (1 1-2 mL reconstituted sterile solution per 100 lb body weight) Treatment should be repeated at 24 hour intervals for a total of three consecutive days Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0 5 to 1 0 mg/lb) should be based on the practitioner's judgement of severity of disease (i e., for respiratory disease extent of elevated body temperature, depressed physical appearance, increased respiratory rate coughing and/or loss of appetite, and for foot rot, extent of swelling, lesion and severity of lameness)

Animal Safety

Results from a five-day tolerance study in normal feeder calves indicated that formulated ceftiofur was well tolerated at 25 times (25 mg/lb/day) the highest recommended dose of 1 0 mg/lb/day for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were intramuscularly administered formulated ceftiofur at 0 (vehicle control) 1 3 5 and 10 times the highest recommended dose of 1.0 mg/lb/day to determine the safety factor There were no adverse systemic effects indicating that the formulated ceftiofur has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg/lb/day) the recommended dose for three times (15 days) the recommended three to five days of therapy The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at 1 and 3 times the highest recommended dose of 1 0 mg/lb/day The histopathological evaluations were conducted at postreatment days 1 3, 7 and 14.

The injection of NAXCEL® Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated However a several square centimeter area of yellow-red discoloration resulting from a single SC injection persisted in many of the cattle beyond 4 5 days post injection Also, one of the animals developed an abscess at the injection site

Residue Warnings Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage and route of administration Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.

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Precautions

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation Attention to hygienic procedures can minimize their occurrence

SWINE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2

Dosage and Administration

Administer to swine by intramuscular injection at the dosage of 1 36 to 2 27 mg ceftiofur/lb (3 0 to 5 0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 pounds of body weight) Treatment should be repeated at 24 hour intervals for a total of three consecutive days

Animal Safety

Results from a five day tolerance study in normal feeder pigs indicated that formulated ceftiofur was well tolerated when administered at 57 mg/lb (more than 25 times the highest recommended daily dosage of 2 27 mg/lb of body weight) for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity

To determine the safety factor and to measure the muscle irritancy potential in swine a safety/toxicity study was conducted Five barrows and five gilts per group were intramuscularly administered to related ceftiofur at 0, 2 27 6 81 and 11 36 mg/lb of body weight for 15 days which is 0, 1 3 times the highest recommended dose of 2 27 mg/lb of body weight/day and 5 times the recommended treatment length of 3 days There were no adverse systemic effects indicating that formulated ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2 27 mg/lb/day for 3 days or at lengths up to 5 times the highest recommended dose for 5 times the recommended length of treatment The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at postreatment days 1 2 3 and 4 By day 15 post injection the muscle reaction was subsiding and at day 15 post injection there was little evidence of muscle damage in any of the pigs in any of the treatment groups

Tissue Residue Depletion

Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney liver and muscle Three tolerances of ceftiofur residues are 0 25 ppm in kidney, 0 5 ppm in liver and 2 0 ppm in muscle

A pivotal tissue residue decline study was conducted in swine In this study pigs received 2 27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney liver and muscle by 4 days after dosing These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

Residue Warnings. When used according to label indications, dosage and route of administration, treated pigs must not be slaughtered for 4 days following the last treatment. Use of dosages in excess of those indicated or by unapproved routes may result in illegal residues in edible tissues

Precautions

The safety of ceftiofur has not been determined for swine intended for breeding

SHEEP USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*

Dosage and Administration

Administer to sheep by intramuscular injection at the dosage of 0 5 to 1 0 mg ceftiofur per pound of body weight (1 2 mL reconstituted sterile solution per 100 lbs body weight) Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0 5 to 1 0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance increased respiratory rate coughing and/or loss of appetite)

Animal Safety

In a 15-day safety/toxicity study in sheep three wether and three ewe lambs per group were given formulated ceftiofur sodium by the intramuscular route 0 (sterile water vehicle) 1, 3 or 5 times the recommended dose of 1 0 mg/lb/day for 3 times the recommended maximum duration of 5 days of treatment There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in sheep Based on examination of injection sites from study days 9, 11, 13 and 15, a low incidence of visual changes and histopathologic findings of mild, reversible inflammation from all groups including the controls indicated that the formulation is a slight muscle irritant.

Residue Warnings Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage and route of administration Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.

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GOAT USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Dosage and Administration

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound of body weight (1–2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Animal Safety

In a 15-day safety-toxicity study 5 lactating does, 5 dry does, and 5 wethers were given formulated ceftiofur by the intramuscular route with 11 mg/kg/day for 15 days. This constitutes 5 times the recommended dose for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in goats.

Residue Warnings: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

HORSE USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.

Dosage and Administration

Administer to horses by intramuscular injection at the dosage of 1.0 to 2.0 mg ceftiofur per pound of body weight (2–4 mL reconstituted sterile solution per 100 lb body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Animal Safety

In a safety study, horses received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1.0 mg/lb/day (50 mg/mL), 3.0 mg/lb/day (100 mg/mL), or 5.0 mg/lb/day (200 mg/mL) of an aqueous solution of ceftiofur sodium for 30 or 31 days. Ceftiofur sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/lb/day for 30 or 31 days. No clinical evidence of irritation was noted at any dose. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3.0 or 5.0 mg/lb/day ceftiofur, and general mild skeletal muscle irritation at the injection sites which resolved by regeneration of muscle fibers.

In a tolerance study, horses received a single daily intravenous infusion of either 0 (saline), 10.0 or 25.0 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for 10 days. The results indicated that ceftiofur administered intravenously at a dose of 10.0 or 25.0 mg/lb/day apparently can change the bacterial flora of the large intestine thereby leading to inflammation of the large intestine with subsequent diarrhea and other clinical signs (loose feces, eating bedding straw, dehydration, rolling or colic and a dull, inactive demeanor). Decreased food consumption, a loss of body weight, hematologic changes related to acute inflammation and stress, and serum chemistry changes related to decreased food consumption and diarrhea were also associated with treatment at these doses. The adverse effects were most severe a few days after dosing was initiated and tended to become less severe toward the end of the 10-day dosing period.

Residue Warnings: Not for use in horses intended for human consumption.

Precautions

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

DOG USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

Dosage and Administration

Administer to dogs by subcutaneous injection at the dosage of 1.0 mg ceftiofur per pound of body weight (0.1 mL reconstituted sterile solution per 5 lbs of body weight). Treatment should be repeated at 24-hour intervals for 5-14 days.

Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No vial closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Animal Safety

Ceftiofur sodium was well tolerated at the therapeutic dose and is safe for the treatment of urinary tract infections in dogs. In the acute safety study, ceftiofur was well tolerated by dogs at the recommended level (1.0 mg/lb) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four females developed thrombocytopenia (15 days) and anemia (36 days). Thrombocytopenia and anemia also occurred at the 3X and 5X dose levels. In the reversibility phase of the study (5X dose), the thrombocytopenia reversed within 8 days, and of the two anemic animals the male recovered within 6 weeks and the female was sacrificed due to the severity of the anemia.

In the 15-day tolerance study in dogs, high subcutaneous doses (25 and 125 times the recommended therapeutic dose) produced a progressive and dose-related thrombocytopenia, with some dogs also exhibiting anemia and bone marrow changes. The hematopoietic changes noted in dogs treated with ceftiofur were similar to those associated with long-term cephalosporin administration in dogs and also man. The hematopoietic effects are not expected to occur as a result of recommended therapy.

Precautions

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

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DAY-OLD CHICKEN USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Dosage and Administration

Administer by subcutaneous injection in the neck region of day-old chicks at the dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Animal Safety

In an acute toxicity study of ceftiofur in day-old chicks, a total of 60 male and 60 female chicks were each given single subcutaneous injections of 10, 100 or 1,000 mg/kg of body weight. Treatment on day 1 was followed by 6 days of observation; body weight was determined on days 1, 4 and 7; and selected hematology parameters were evaluated on day 4. No meaningful differences were noted among the treated and control groups of chicks for the parameters evaluated. Histopathologic evaluation of all deaths and chicks surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 20 times (100 mg/kg) the intended highest use dosage.

DAY-OLD TURKEY POULTS USE INFORMATION

Indications

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.

Dosage and Administration

Administer by subcutaneous injection in the neck region of day-old turkey poults at the dosage of 0.17 to 0.5 mg ceftiofur/poult. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

Animal Safety

In an acute toxicity study of ceftiofur in day-old turkey poults, a total of 30 male and 30 female poults were each administered single subcutaneous injections of 100, 400 or 800 mg/kg body weight. Injection on day 1 was followed by 6 days of observation; body weight on days 1, 4, and 7; and selected hematology parameters on day 4. No meaningful differences were noted between the treated groups at 100 or 400 mg ceftiofur/kg and a negative control group for the parameters evaluated. Histopathologic evaluation of deaths and poults surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 50 times (400 mg/kg) the highest use dosage. A dose of 800 mg/kg (100 times the intended highest use dosage) was toxic, resulting in clinical signs and deaths accompanied by gross and microscopic morphologic tissue alterations.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.
Restricted Drug (California) — Use Only as Directed.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or obtain a material safety data sheet, call 1-800-253-8600.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

HOW SUPPLIED

NAXCEL Sterile Powder is available in the following package sizes:

1 gram vial	**NDC** 0009-3362-03
4 gram vial	**NDC** 0009-3362-04

[1] National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

NADA # 140-338, Approved by FDA

Mfd. for. **Pharmacia & Upjohn Company**
Kalamazoo, MI 49001, USA

By: SmithKline Beecham Corporation
Conshohocken, PA 19428

Revised February 2004

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Pfizer

Composition Unit 2566

Black

COMPOSITION ORDER # 23046	PRODUCT NAXCEL		COPY CODE # 814 055 524B	
CCS # 3362-03	NDC #	EDP # 692432	ITEM Insert	
BOTTLE #	SIZE 20 x 10"	FOLDED SIZE 2.5 x 1.25"	DRAWING # PD2170	DRAWING REVISION #
ADDITIONAL INFORMATION		DATE 2-26-04	TYPESET BY KL	